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EXAMINER
BRADLEY, CHRISTINA

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,861	GENKIN ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-13 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1, 4, 6-13 and 15 are pending. Claims 2, 3, and 14 were cancelled in the response filed 12/26/2008. Thus, all rejections of claims 2, 3 and 14 are now moot. Claim 15 was added and claims 1, 4, 6, 8 and 9 were amended in the response filed 12/26/2008.

Withdrawn Claim Objections

2. The previously issued objections to claims 1-14 are withdrawn in light of the amendment filed 12/26/2008.

New Claim Objection

3. Claims 1, 4 and 6-13 are objected to because of the following informalities: "foregoing cancers and diseases" should be "aforementioned cancers and diseases" or "said cancers and diseases". Alternatively, the claim could be written as "introducing a treatment agent into a blood circulating system of a patient in need thereof". Appropriate correction is required.

Withdrawn Claim Rejections - 35 USC § 112, second paragraph

4. The following rejections under 35 U.S.C. 112, second paragraph, are withdrawn in light of the amendment filed 12/26/2008.

The rejection of claims 1, 4 and 6-13 regarding the limitation "said treatment agent destroys extracellular DNA said blood of said cancer patient " in claim 1 is withdrawn because claim 1 as amended requires a specific hydrolytic activity of the administered DNAse I.

The rejection of claims 1, 4 and 6-13 regarding the relationship between the extracellular DNA and blood is withdrawn because the word "in" is inserted after DNA in line 6.

The rejection of claims 1, 4 and 6-13 regarding the patient population to which the treatment agent is administered is withdrawn because the claim requires that the patient be diagnosed with the cancer.

The rejection of claim 4 regarding the limitation "wherein said treatment is carried out during no less than 48 hours uninterruptedly" is withdrawn.

The rejection of claim 9 regarding the limitation "wherein the treatment is carried out for a term of life" is withdrawn.

Maintained Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 4, 6-13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1 and 15 recite the limitation "certain oncological diseases". The specification does not define the term "certain" in a manner that clearly establishes the metes and bounds of the genus oncological diseases. The amendment filed 12/26/2008 did not delete this claim term and the rejection was not otherwise traversed.

8. Claim 1 recites the limitation a method for treatment of lung carcinoma, breast cancer, gastric, and colon cancer, kidney cancer…" It is not clear from this construction whether gastric cancer and colon cancer are separate alternatives of disease to be treated by the method or whether gastric and colon cancer is one type of specific condition in which the patient is

suffering from cancer of both locations. The amendment filed 12/26/2008 did not delete these claim terms and the rejection was not otherwise traversed.

Maintained Claim Rejections - 35 USC § 112, first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 4, 6-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Erlich carcinoma in mice, lung carcinoma in humans and malignant and low differentiated lymphoma metastasized in the liver of humans by administering DNAse to patients, and for treating Erlich carcinoma in mice by administering DNAse and anti-DNA antibodies, does not reasonably provide enablement for treating all other oncological diseases with DNAse with or without the addition of modify agents or other DNA binding agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and are as follows:

The Nature of the Invention

11. The invention is drawn to a method for treating oncological diseases by administering DNAse as a blood extracellular DNA destroying agent.

The State of the Prior Art and its Predictability or Unpredictability

12. Anker *et al.* (*Leukemia*, **2001**, *15*, 289-91 teach that circulating DNA levels are higher in the blood of cancer patients than in healthy controls (page 289). The prior art does not teach or suggest that cancer can be treated by reducing the circulating DNA levels.

13. The prior art of Young (WO 2001074905) and Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70) teaches that ovarian cancer can be treated by intravenous injection of the DNaseI/huHMFG-1 Fab fusion protein and that DNAse I reduces liver metastasis, respectively, but does not teach that the mechanism of action of the DNAse I is the destruction of extracellular DNA in the blood stream of the cancer patients. There is no guidance in the prior art on how to use DNAse to destroy extracellular DNA to effectively treat cancer.

14. The cancer treatment and biopharmaceutical art is highly unpredictable, as underscored Ulrich & Friend (*Nature*, **2002**, *1*, 84-88), Ashton (*Nature Biotech*, **2001**, *19*, 307-311), and Gibbs *et al.* (*Science*, **2000**, *287*, 1969-1973) who discuss the difficulties in drug development and the high failure rates of candidate drugs in clinical trials.

The Relative Skill of Those in the Art

15. It is not within the ordinary skill of the art to treat cancer by destroying extracellular DNA in the circulating blood stream of cancer patients.

The breadth of the claims

16. The claims are exceptionally broad with respect to the diseases to be treated. Oncological diseases include all types of cancer known to affect humans and animals.

The Amount of Direction or Guidance Presented and the Presence of Working Examples

17. The specification presents working examples of the treatment of three oncological diseases: Erlich carcinoma in mice (examples 1 and 2), lung carcinoma in humans (example 3) and malignant, low differentiated lymphoma metastasized in the liver of humans (example 4). In each case, the administration of DNAse resulted in a reduction in circulating extracellular DNA and tumor. The specification fails to provide working examples for the treatment of any additional oncological diseases.

18. The specification presents only one working example of an "agent binding the blood extracellular DNA", polyclonal serum containing anti-DNA antibodies (example 6). The specification fails to define agent binding the blood extracellular DNA", and to provide guidance on how to isolate other agents with the claimed ability to bind extracellular DNA.

19. The specification fails to present a single working example involving the administration of a modifying agent. Example 7 describes the effect of "modificating agents" on the pathogenic properties of DNA that has been extracted from plasma, and then subsequently administered to patients, but does not describe the effect of directly administering the "modificating agent".

The Quantity of Experimentation Necessary

20. The extent of guidance and working examples presented in the specification is insufficient to enable the full scope of the claimed methods. One cannot extrapolate the teachings of the specification, which are limited to three narrow conditions, to the full scope of the claims, which are broadly drawn to methods for treating all malignant tumors and oncological diseases by targeting extracellular DNA with DNAse. There is no evidence in the prior art or the specification to suggest that the destruction of extracellular DNA in the blood of cancer patients is a universally effective means to combat the disease. As a result the skilled

artisan would be burdened with testing DNAse in a large number of models for different oncological diseases. Furthermore, the skilled artisan would be burdened with testing and developing compounds representative of the full scope of binding agents in claim 10. The experimentation required represents years of inventive effort. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Response to Arguments Filed 12/26/2008

21. To traverse this rejection, Applicant described pilot clinical trials of DNAse enzyme monotherapy in patients with malignant melanoma, breast cancer, gastric cancer, colon cancer, pancreatic adenocarcinoma, lung cancer, colon cancer, recurrent renal cancer, recurrent rectal carcinoma and lung cancer. All patients demonstrated stabilization of the disease assessed by spiral CT scan and significant increase in Karnofsky performance score, and some patients showed shrinkage of metastic nodules.

22. This evidence is insufficient to overcome the scope of enablement rejection because the specification must be enabling as of the filing date. The clinical trial data referred to in the arguments filed 12/26/2008 represents post-filing date information that would not have been available to the skilled artisan at the time of filing. See MPEP § 2164.05. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. For this reason, the rejection is maintained.

23. Claims 1, 4, 6-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

24. Originally filed claim 1 was drawn to a method of treating oncological diseases by introducing a blood extracellular DNA destroying agent. In the response filed 06/24/2008, claim 1 was amended to a method of treating lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma, malignant lymphoma and certain oncological diseases. Thus, the scope of the diseases to be treated by the method of claim 1 has been narrowed from all oncological diseases to lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma, malignant lymphoma and certain oncological diseases. The specification as originally filed fails to support this amendment. This is a new matter rejection.

25. Applicant correctly argues in the response filed 12/26/2008 that lung carcinoma and malignant low differentiated lymphoma are supported in examples 3 and 4, respectively, of the originally filed specification.

26. In contrast, the claim terms breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma and certain oncological diseases do not appear in the specification as originally filed and are therefore not explicitly supported in the specification. Although one of ordinary skill in the art would recognize that breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma, and certain oncological diseases

are species in the genus of oncological diseases, one of ordinary skill in the art would not select these specific diseases for treatment with DNAse from amongst the entire genus. There is no suggestion or guidance in either the specification or prior art that would lead to this sub-genus. Therefore, the amendment is not implicitly supported in the specification as originally filed.

27. Applicant did not specifically traverse the rejection with respect to breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma and certain oncological diseases. Therefore, the rejection is maintained.

Withdrawn Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Young (WO 2001074905) is withdrawn in light of the amendment filed 12/26/2008 which requires a dose and regiment which provides blood plasma DNA hydrolytic activity to exceed 150 Kunitz units per liter of plasma during more than 12 hours in total within 24 hours. Young does not teach a specific dose or regiment. The instant specification provides evidence that not every dose of DNAse I destroys extracellular DNA. See Table 1 and paragraph 0041. Therefore, a DNA hydrolytic activity exceeding 150 Kunitz units per liter of plasma during more than 12 hours in total within 24 hours is not necessarily present in the teaching of Young.

30. The rejection of claims 1 and 10 under 35 U.S.C. 102(b) as being anticipated by Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70) is withdrawn in light of the amendment filed 12/26/2008

which requires a dose and regiment which provides blood plasma DNA hydrolytic activity to exceed 150 Kunitz units per liter of plasma during more than 12 hours in total within 24 hours. Sugihara *et al.* teaches a dose of 0.1 Kunitz units which falls outside of the claimed range.

New Claim Rejection - 35 USC § 102

31. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

32. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70). New claim 15 is drawn to a method of treating certain oncological diseases comprising administering DNAse enzyme into the circulating blood system of a cancer patient, wherein said DNAse destroys extracellular DNA and is administered in doses sufficient to provide an electrophoretic profile change in the extracellular DNA as measured by pulse-gel electrophoresis.

33. On p. 67, col 1, para. 2, Sugihara *et al.* explicitly state that DNase I was administered to mice having malignant liver tumors by intravenous injection (i.e. into the circulating blood system of the mice) at a dose of 0.1 Kunitz units. The subject in the study reported by Sugihara *et al.* is a spontaneous metastasis model using the L5178Y-ML cell line, which is derived from a murine T-lymphoma cell line and which metastasizes predominantly to the liver after subcutaneous injection (p. 66, cols 1-2). DNAse 1 (0.1 U per mouse) was injected intravenously at days 3, 5 and 5 or 5, 6 and 7 after tumor cell inoculation (p. 67, col 1). In all mice implanted with L5178Y-ML cells, a tumor mass developed and in all cases severe metastasis in the liver

but no other organs was observed (p. 67, col 2). All animals were sacrificed on day 14 and the liver weight and subcutaneous tumor size were measured. DNAse I treatment significantly reduced the liver weight, and therefore the extent of liver metastasis, compared to the control but did not have any effect on the primary tumor size (Table II). In addition, in DNAse-I treated group (Figure 1c, 1d), the numbers of metastatic foci were fewer and their sizes smaller, as compared to the control (p. 67, col 2). Sugihara *et al.* write on p. 69:

> In addition, the failure of primary tumor resection at 5 days to prevent liver metastasis indicated the presence of tumor cells with metastatic potency in the circulation at least 5 days after subcutaneous cell inoculation. These results indicated that DNAse I interfered with tumour cells in the circulation. How DNase I interferes with tumour cells is not yet clear.

Sugihara *et al.* speculate on p. 70 that the role of DNAse I may be to breakdown DNA circulating in the bloodstream that acts as a scaffold for tumour cell aggregation.

With respect to claim 15, Sugihara *et al.* teaches a method of administering DNAse I to the circulating blood system of a patient having an oncological disease. The DNAse I treatment has a significant effect on liver metastasis. Sugihara *et al.* do not explicitly teach that the mechanism of action of the DNAse I treatment is the destruction of extracellular DNA or a change in the electrophoretic profile of extracellular DNA. Because the active method steps of the instant claim are taught in the prior art, this effect or result is inherently met.

MPEP § 2112.02 states: "The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082,

1090, 197 USPQ 601, 607 (CCPA 1978)" In the instant case, the preamble of claim 15 is met by the teaching of Sugihara *et al.* That is, the oncological disease, liver cancer, is treated by the administration of DNAse I to the circulating blood system of the cancer patient. The mechanism of action (i.e. destruction of extracellular DNA) recited in the claim constitutes a result or property of DNAse I that is inherently taught by Sugihara *et al.* rather than a new use of the DNAse I. The DNAse I of Sugihara *et al.* is administered to the circulating blood system of the mice bearing subcutaneous tumour derived from T-lymphoma cell lines, and therefore comes in contact with extracellular DNA in the blood system as an inherent aspect of the method. There is nothing on record to suggest that the DNAse I would be incapable of hydrolyzing said extracellular DNA. It is not necessary for Sugihara *et al.* to recognize or appreciate the mechanism of action of the DNAse I in order to anticipate claim 15. Because the active method steps are taught by Sugihara *et al.* and the destruction of DNA is a result or property of DNAse I, the claim is anticipated.

34. In the response filed 12/26/2008, Applicant traverses the rejection on the grounds that Sugihara limits its teaching to theory and its method to DNase treatment in the microvasculature of the liver or removing primary tumor mass and DNase treatment. This is not found to be persuasive. On p. 67, col 1, para. 2, Sugihara *et al.* explicitly state that DNase I was administered to mice having malignant liver tumors by intravenous injection (i.e. into the circulating blood system of the mice).

35. In the response filed 12/26/2008, Applicant traverses the rejection on the grounds that Sugihara *et al.* did not recognize or understand the role of inactivation of free circulating

extracellular DNA in cancer treatment. This is not persuasive in light of the fact that Sugihara *et al.* teach the active method steps of the claim. See discussion of MPEP § 2112.02.

36. In the response filed 12/26/2008, Applicant argues that 666 Knuitz Unit per mouse per day is required to destroy DNA. This argument is not persuasive with respect to claim 15 because a) claim 15 does not specify a dose; and b) Applicant's arguments do not indicate that 666 Kunitz Unit per mouse per day is required to produce a change in the electrophoretic profile of extracellular DNA.

Withdrawn Claim Rejections - 35 USC § 103

37. The rejection of claims 1, 4, 6 and 9 under 35 U.S.C. 103(a) as being unpatentable over Young (WO 2001074905) is withdrawn in light of the amendment and arguments filed 12/262/008.

Maintained Claim Rejections - 35 USC § 103

38. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

39. The rejection of claims 1, 4, 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70). The teachings of Sugihara *et al.* are described above. Sugihara *et al.* do not teach the specific dosage regiments recited in claims 1, 4, 6 and 9. MPEP § 2144.05 states: "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In the instant case, given the teaching in Sugihara *et al.* that DNAse I can be used to prevent liver metastases (p. 70):

> The most important result of the present study must be the life span-prolongation effect of DNAse I in combination with surgical treatment of the primary lesion. Surgical removal of the subcutaneously inoculated tumour alone had no prolonging effect and all mice died from micrometastases in early periods. Many combinations of DNAse I treatment with other tumour therapies are possible. Thus, DNAse I treatment may potentially be useful in the prevention of cancer metastasis.

the skilled artisan would have been motivated to optimize dosage and treatment schedule through routine optimization. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

40. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70), as applied to claims 1, 4, 6 and 9 above, in further view of Shak *et al.* (*Proc. Natl. Acad. Sci.*, **1990**, *87*, 9188-9192). Sugihara *et al.* does not teach the use of human recombinant DNAse. Shak *et l.* teach the cloning, expression and characterization of human recombinant DNAse I. It would have been obvious to substitute the human recombinant DNAse I taught by Shak *et al.* when applying the method of administering bovine DNAse I taught by Sugihara *et al.* to human cancer patients. The skilled artisan would have been

motivated to do so based on the teaching of Shak *et al.* that the use of the human enzyme could reduce side effects observed with the use of the bovine enzyme (p. 9188, col. 2). There would have been a reasonable expectation of success given that the enzymes posses the same structure and activity (p. 9189-91). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

41. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70), as applied to claims 1, 4, 6 and 9 above, in further view of Leland *et al.* (*Chem. & Bio.*, **2001**, *8*, 405-13). Sugihara *et al.* does not teach the use of ribonuclease to treat oncological disease. Leland *et al.* teach that onconase, a ribonuclease, is in clinical trials as a cancer chemotherapeutic (abstract). MPEP § 2144.06 states: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." Therefore, it would have been obvious to combine the DNAse of Sugihara *et al.* with the RNAse of Leland *et al.* given that both agents have anticancer effects.

Withdrawn Double Patenting Rejections

42. The rejection of claims 1 and 5 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/564,609 is withdrawn in light of the terminal disclaimer filed 06/24/2008.

43. The rejection of claims 1 and 5 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 13 of copending Application No. 10/546,615 is withdrawn in light of the terminal disclaimer filed 06/24/2008.

Conclusion

44. No claims are allowed.

45. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

46. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:00 P.M.

48. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

49. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb